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Analysis of Lymph Node Metastasis in Early Gastric Cancer: Rationale of Limited Surgery

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Background: Since the majority of patients with early gastric cancer show long-term survival after surgery, a special attention must be directed to preserving gastric function in these patients. Little is known about the protocol of surgical treatment appropriate for early gastric cancer patients. This study was designed to determine the appropriate surgical procedure for early gastric cancer.

Methods: The clinicopathologic features of 52 patients with node-positive early gastric cancer were reviewed retrospectively from hospital records between 1969 and 1994 and were compared with those of 582 patients with node-negative early gastric cancer. Nodal status of positive nodes in the 52 cases was investigated.

Results: Depth of invasion, lymph vessel invasion, and tumor size were associated with lymph node metastasis. Node-positive patients with early gastric cancer had a poorer survival rate than node-negative patients ($P < 0.05$). Patients with five or more positive nodes and positive nodes distant from the common hepatic artery showed an extremely poor prognosis.

Conclusions: The surgical procedures most appropriate for the treatment of early gastric cancer are as follows: (1) local gastric resection without lymphadenectomy for mucosal cancers of <2 cm in diameter and for elevated submucosal cancers of <1 cm in diameter, (2) gastrectomy with dissection of the perigastric nodes, the nodes along the left gastric artery and the common hepatic artery, for the treatment of other early gastric cancers. J. Surg. Oncol. 64:42–47

KEY WORDS: early gastric cancer; lymph node metastasis; lymph node dissection; surgery

INTRODUCTION

Extensive lymphadenectomy, the conventional treatment in Japan for the last two decades, has contributed to the improved survival of patients with early gastric cancer [1–3]. However, this procedure is associated with poor quality of life after surgery. A recent trend in the surgical treatment of early gastric cancer patients in Japan has been to limit surgery such that a complete cure is achieved and the patient's quality of life is improved [4–6]. The rate of lymph node metastasis in early gastric cancer varies from 3% to 20% [7] and the average is no more than 10%, which indicates that lymphadenectomy is actually required for only 10% of patients with early gastric cancer, but not for the remaining 90%.

This finding suggests that surgeons should not perform extensive lymphadenectomy in the treatment of every patient with early gastric cancer. To avoid unnecessary lymphadenectomy, the anatomical distribution of regional lymph node involvement must be identified before selection of the surgical procedure. However, it is very difficult to pre- or intraoperatively discriminate cancerous nodes from normal nodes. There have been various attempts to improve the accuracy of lymph node involvement [8–11], with generally unsatisfactory results. At

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present, lymph node involvement is predicted from retrospective clinicopathologic data obtained from previously resected early gastric cancers, and the appropriate surgical procedures are chosen accordingly. This study was designed to determine the clinicopathologic characteristics of node-positive early gastric cancer and to assist in delineating the extent of lymph node dissection most appropriate for the treatment of early gastric cancer.

MATERIALS AND METHODS

From 1969 to 1994, a total of 634 patients with early gastric cancer were admitted to the First Department of Surgery, Kyoto Prefectural University of Medicine, and were enrolled in this study. Early gastric cancer was defined as a lesion in which the depth of invasion was limited to the mucosa or to the mucosa and submucosa, regardless of the presence or absence of lymph node metastasis [12]. Their clinicopathologic characteristics were studied retrospectively based on a review of hospital records and were compared to 582 early gastric cancers without lymph node involvement. The macroscopic and microscopic classification of early gastric cancers was based on the general rules for Gastric Cancer Study in Japan [12]. Histopathological examinations were performed on the primary lesions using serial sections to determine the depth of cancer invasion and other histologic features and on the resected lymph nodes using three central sections to confirm the presence of metastasis. All resected regional lymph nodes were subject to histopathologic examination.

Cumulative survival rates were calculated by the Kaplan-Meier method. Patients who died of diseases unrelated to gastric cancer were excluded from this analysis. All data from both groups were analyzed by a generalized Wilcoxon test [13]. Other statistical analyses were performed by the Chi-square test and Student's t-test. Multivariate analysis by logistic regression adjustment [14] was performed to determine the independent risk factors for lymph mode metastasis. A P value of <0.05 was considered to be statistically significant.

RESULTS

The clinicopathologic details of node-positive and node-negative early gastric cancers are summarized in Table I. Lymph node metastasis was observed pathologically in 52 of 634 patients with early gastric cancer (8.2%).

Tumor Size and Location

Tumor size of the node-positive cancers was larger than that of the node-negative cancers ($P < 0.005$). There was no difference in tumor location between node-positive and node-negative cancers.

Macroscopic Types

The macroscopic type of the primary tumors was classified as follows: (a) I, protruded, (b) IIa, superficial elevated, (c) IIc, superficial depressed, (d) III, excavated, (e) early gastric cancer simulating advanced cancer, (f) IIa + IIc combination of (b) and (c); (g) IIc + III, combination of (c) and (d). There was no statistical difference in the rates of elevated and depressed lesions between node-positive and node-negative cancers. Type (e), early gastric cancer simulating advanced cancer, was more common in node-positive cancers than in note-negative cancers ($P < 0.005$).

Surgery and Chemotherapy

There was no difference in the extent of stomach resection between the two groups. More extensive lymph node dissection was performed on patients with node-positive adenocarcinomas ($P < 0.05$). Of the 31 patients with multiple metastatic nodes, 16 underwent postoperative chemotherapy: a 5-Fu equivalent to 150–300 mg was orally administered every day over a 1–2-year period.

Histologic Types

Histologic type was divided into two subtypes: (1) intestinal type including well- or moderately differentiated and papillary adenocarcinoma, and (2) diffuse type including poorly differentiated, undifferentiated, mucinous, and signet ring cell adenocarcinomas. There was no difference in histologic type between node-positive and node-negative cancers.

Depth of Invasion

Submucosal invasion was more common in node-positive cancers than in node-negative cancers ($P < 0.005$).

Vascular and Lymphathic Invasion

Lymph vessel invasion was more common in node-positive adenocarcinomas than in node-negative adenocarcinomas ($P < 0.005$). There was no difference in vascular invasion between the two groups.

Multivariate Analysis

In single variate analysis, there was a significant difference in tumor size, depth of invasion, or lymphatic invasion by cancer cells between the node-positive and node-negative early gastric cancers. The logistic regression adjustment revealed that depth of invasion and lymphatic invasion by cancer cells, but not tumor size, were independent risk factors for lymph node metastasis (Table II).

TABLE I. Clinicopathologic Findings in Patients With Early Gastric Cancer With or Without Lymph Node Metastasis

Variable	Node-positive (percentage)	Node-negative (percentage)	*P* value
Number	52	582	
Gender			N.S.
Male	38 (73.1)	398 (68.4)	
Female	14 (26.9)	184 (31.6)	
Age (mean ± SD)	60.46 ± 12.0	59.22 ± 11.7	N.S.
Location			N.S.
Upper	5 (9.6)	52 (8.9)	
Middle	20 (38.5)	289 (49.7)	
Lower	27 (51.9)	222 (38.1)	
Unknown	0	19 (3.3)	
Tumor size			$P = 0.000002$
⩽2.0	8 (15.4)	257 (44.2)	
2.1 ⩽ 4.0	21 (40.4)	233 (40.0)	
4.1 ⩽ 6.0	15 (28.8)	68 (11.7)	
6.1⩽	8 (15.4)	16 (2.7)	
Unknown	0	8 (1.4)	
Macroscopic type			
Elevated	11 (21.2)	116 (19.9)	
I	3	25	
IIa	1	37	
IIa + IIc	7	54	
Depressed	23 (44.2)	340 (58.4)	
IIc	16	254	
IIc + III	7	86	
Advanced	14 (26.9)	20 (3.4)	$P < 0.005$
Others	4 (7.7)	97 (16.7)	
Unknown	0	9 (1.5)	
Gastric resection			N.S.
Total	6 (11.5)	48 (8.2)	
Distal	45 (86.5)	498 (85.6)	
Proximal	1 (1.9)	24 (4.1)	
Partial	0	12 (2.1)	
Lymph node dissection			$P < 0.05$
limited			
D0	0	6 (1.0)	
D1	8 (15.4)	165 (28.4)	
extensive			
D2	43 (82.7)	404 (69.4)	
D3	1 (1.9)	7 (1.2)	
Depth of invasion			$P < 0.0000001$
Mucosa	2 (3.8)	324 (55.7)	
Submucosa	50 (96.2)	258 (44.3)	
Histologic type			N.S.
Intestinal	30 (57.7)	348 (59.8)	
Diffuse	18 (34.6)	195 (33.5)	
Unknown	4 (7.7)	39 (6.7)	
Lymphatic vessel invasion			$P < 0.0000001$
Positive	25 (48.1)	31 (5.3)	
Negative	23 (44.2)	365 (62.7)	
Unknown	4 (7.7)	186 (32.0)	
Vascular invasion			N.S.
Positive	6 (11.5)	10 (1.7)	
Negative	39 (75.0)	381 (65.5)	
Unknown	7 (13.5)	191 (32.8)	
Causes of death			
Peritonitis carcinomatosis	2	1	
Lymphangitis carcinomatosis	2	1	
Liver metastasis	3	2	
Lung metastasis	1	2	
Local recurrence	0	0	
Unknown recurrence	3	5	
Others diseases	4	58	

N.S. = not significant.

TABLE II. Logistic Regression Analysis for Variables Associated With Lymph Node Metastasis in Early Gastric Cancer

Explanatory variable	Regression coefficient	*P* Value
Depth of invasion	0.947	0.00015
Lymph vessel invasion	1.803	$P < 0.000001$
Tumour size	0.012	0.932

Anatomical Distribution of Lymph Node Metastasis

Lymph node station is shown in Figure 1. [12], and the anatomical distribution of lymph node metastasis is shown in Figure 2. Positive nodes were found predominantly in the perigastric regions adjacent to the tumors. In 13 patients, these were detected in the following regions: along the left gastric artery, around the common hepatic artery, along the celiac artery, around the hepatoduodenal ligament, and/or the abdominal aorta. A single positive node was found in 21 cases, whereas multiple positive nodes (5 or more) were found in 11 cases (Table III). The mean number of positive nodes was 2.64 per patient. Of the 52 node-positive adenocarcinomas, 13 cases were intraoperatively diagnosed as node-positive (25%). There was no lymph node metastasis in early gastric cancer that satisfied the following criteria: (1) mucosal cancer of <2 cm in diameter, and (2) elevated submucosal cancer of <1 cm in diameter.

Survival

Patients with node-positive early gastric cancers showed a poorer survival rate than those with node-negative early gastric cancers ($P < 0.05$, Fig. 3). Eleven node-positive patients died after a recurrence of cancer, as listed in Table IV. Of 11 cases with five or more positive nodes, six died of recurrence, whereas five of the 31 cases with one or two positive nodes died of recurrence. Lymph node recurrence was found in three patients who had five or more positive nodes. They were simultaneously complicated by peritoneal or liver metastasis and died of these complications.

Relationship between survival and anatomical distribution of metastatic nodes. Of the 11 fatal cases with lymph node metastasis, six had involvement in only one of the six of perigastric lymph node stations, and the remaining five cases had involvement in multiple stations, including lymph nodes along and/or more distant from the left gastric artery, such as lymph nodes around the common hepatic artery and the celiac artery (Table IV). Of the 10 cases with involvement in lymph nodes along the left gastric artery, six cases survived and four cases died of recurrence. Of the six cases with involvement in lymph nodes around the common hepatic artery, two survived and four died of recurrence. The four fatal cases had lymph node metastasis in both regions along the left gastric artery and common hepatic artery and were simultaneously complicated by positive nodes in regions distant from the common hepatic artery. In contrast, lymph node metastasis was confined to the left gastric and/or common hepatic artery in the eight surviving cases.

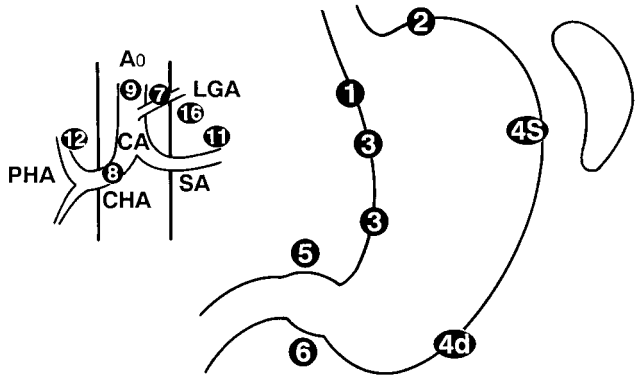

Fig. 1. Station numbers of regional lymph nodes. Circles indicate station numbers of regional lymph node. 1, right cardial; 2, left cardial; 3, lesser curvature; 4s and 4d, right and left gastroepiploic arteries; 5, suprapyloric; 6, infrapyloric; 7, left gastric artery; 8, common hepatic artery; 9, celiac artery; 11, splenic artery; 12, hepatoduodenal ligament; 16, paraaortic.

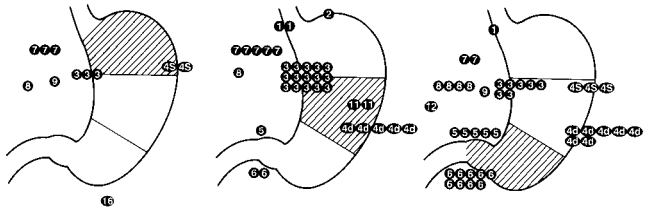

Fig. 2. Anatomical distribution of metastatic lymph nodes according to the location of the tumor. left, upper third; middle, middle third; right, lower third. Circles indicate metastates to regional lymph nodes.

TABLE III. Number of Metastatic Lymph Nodes Per Patient

No. of positive nodes	No. of cases
1	21
2	10
3	5
4	5
5	5
6–10	5
More than 10	1

DISCUSSION

Our study demonstrated that patients with node-positive early gastric cancer had a poorer survival rate than patients with node-negative early gastric cancer. Of the several recurrence types in early gastric cancer, the most predominant is hematogeneous metastases in the liver, lung, or bone [15]. In general, lymph node recurrence is rare in early gastric cancer, and when it occurs it

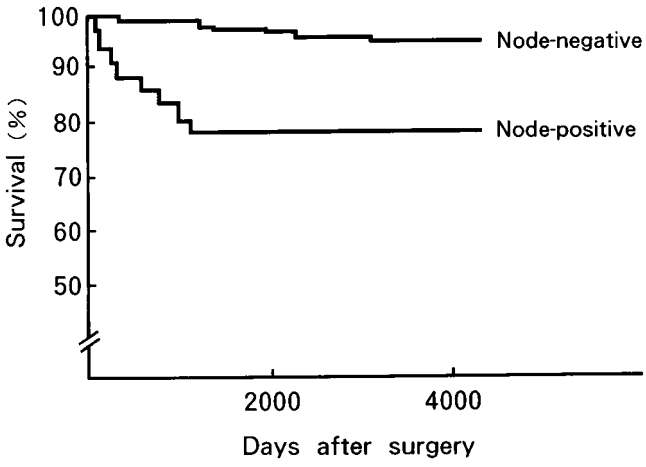

Fig. 3. Survival curves of patients with node-positive and node-negative early gastric cancers. Patients with node-positive early gastric cancer showed a poorer survival rate than those with node-negative early gastric cancer ($P < 0.05$).

is always complicated by hematogeneous metastases or peritoneal dissemination. The present study also found that the three patients who showed lymph node recurrence died of peritoneal metastasis or liver metastasis. Lymph node recurrence is not an independent prognostic factor, but it is associated with hematogeneous or peritoneal cancer recurrence.

We demonstrated the following clinicopathologic factors to be correlated with lymph node metastasis: (1) submucosal invasion, (2) lymphatic invasion by cancer cells, and (3) large tumor size. Single variate analysis showed that all of these factors correlated well with the occurrence of lymph node metastasis. This observation is consistant with previous reports by other investigators [4,16]. However, multivariate analysis revealed that the former two factors, but not the latter one, are independent risk factors for the occurrence of lymph node metastasis. Lymph node metastasis is more likely to develop with early submucosal gastric cancer than with mucosal cancer, because the submucosal layer of the stomach is rich in lymphatic capillaries. Large tumors are more frequently associated with submucosal invasion and lymphatic invasion than small tumors, which in turn is associated with a higher incidence of lymph node metastasis. Thus tumor size itself is not an independent predictor for lymph node metastasis.

The lack of accurate methods for diagnosing lymph node metastasis has prompted Japanese surgeons to evaluate clinicopathologic factors that might be useful for predicting the likelihood of lymph node metastasis. Several investigators [4,7] have demonstrated a number of criteria that are not associated with lymph node metastasis: (1) mucosal cancer, (2) small tumor size, and (3) elevated lesions. These criteria are almost consistent among reports described previously, although a few variations are found. Our study demonstrated that there was no lymph node metastasis in cases of mucosal cancer <2 cm in diameter or in cases of elevated submucosal cancer <1 cm in diameter. Limited surgery, which involves the local resection of the stomach without lymphadenectomy, is indicated for early gastric cancers that satisfy the criteria mentioned above. This type of surgery, however, is not applicable for early gastric cancer that does not satisfy these criteria.

To determine the surgical treatment most appropriate for early gastric cancers that do not meet these criteria, we investigated the relationship between patient survival and the anatomical distribution of lymph node involvement. Patients in whom lymph node metastasis was confined to perigastric nodes, the nodes along the left gastric artery, and/or the nodes along the left gastric artery survived >5 years after surgery. In contrast, patients with metastases in the nodes along the left gastric artery and common hepatic artery died of hematogeneous or peritoneal recurrence when they were complicated by positive nodes in regions distant from the common hepatic artery. The latter observation suggests that tumors that develop metastases in lymph nodes distant from the common hepatic artery cannot be eradicated by gastrectomy with extensive lymph adenectomy alone. Thus we conclude that lymphadenectomy for early gastric cancer that does not meet the criteria for local resection of the stomach should be confined to the dissections of perigastric nodes, nodes along the left gastric artery, and those around the common hepatic artery.

Whether or not postoperative chemotherapy should be performed in cases of early gastric cancer remains questionable. We did not typically perform postoperative chemotherapy on patients with node-negative early gastric cancer or those with early gastric cancers complicated by one or two positive nodes. Of 11 patients with five or more positive lymph nodes, six died of recurrence. The high fatality of this group may indicate that early gastric cancer patients with five or more positive nodes show an extremely poor prognosis and require more intensive and powerful chemotherapy. These cancers were considered to be extremely malignant in biological behavior, although we were unable to predict this biological behavior.

Overall, a poorer prognosis was demonstrated in patients with node-positive early gastric cancer. Patients with five or more positive nodes and positive nodes distant from the common hepatic artery revealed an extremely poor prognosis. The three factors most strongly associated with lymph node metastasis in cases of early gastric cancer were: large tumor size, submucosal invasion, and lymphatic involvement. The following surgical criteria were delineated for patients with early gastric cancer: (1) local gastric resection without lymphadenectomy is recommended for mucosal cancers <2 cm in

TABLE IV. Details of 11 Fatal Cases With Node-positive Early Gastric Cancer

Variable	Age/sex	Depth of invasion[a]	Histology[b]	Extent of lymph adenectomy[c]	Sites of positive nodes (number of positive nodes)[d]	Recurrence type	Survival time
1	59/M	sm	tub2	D3	No3 (2)	undefined	2yr, 11mo
2	52/M	m	tub1	D2	No4 (6)	liver metastasis	10mo
3	32/M	sm	por	D2	No6 (2)	undefined	3yr, 3mo
4	67/F	sm	tub2	D2	No6 (1)	lung metastasis	5mo
5	71/M	sm	por	D2	No6(1)	undefined	2yr, 3mo
6	70/M	sm	tub2	D2	No3,4 (5)	liver metastasis	1yr, 9mo
7	73/M	sm	por	D2	No5,7,8,9 (6)	lymphangitis carcinomatosis	8yr, 8 mo
8	79/F	sm	por	D2	No3,7,8,9,16 (6)	peritonitis carcinomatosis	5mo
9	61/F	sm	tub1	D2	No3,7,8,11 (5)	peritonitis carcinomatosis	9mo
10	69/M	sm	tub1	D2	No3 (1)	liver metastasis	4mo
11	55/M	sm	sig	D2	No3,7,8,9,11,12 (15)	lymphangitis carcinomatosis	11yr, 5mo

[a]sm: submucosal; m: mucosal.
[b]tub 2: moderately differentiated; tub1: well differentiated; por: poorly differentiated; sig: signet ring cell.
[c]D1: dissection of Group 1 nodes (no1–6); D3 dissection of Group 3 nodes (No1–14); D2: dissection of Group 2 nodes (No1–9).
[d]No: station number.

diameter and for elevated submucosal cancers <1 cm in diameter, and (2) gastrectomy with dissection of the perigastric nodes, the nodes along the left gastric artery, and those along the common hepatic artery is recommended for other early gastric cancers.

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